INTRODUCTION

Peripheral vascular disease is a major health care problem in an aging society. An important compensatory response to atherosclerotic obstructive arterial disease is collateral development, a complex process requiring that multiple genes coordinately express their products in an appropriate time-dependent manner *(Mi Hyang et al., 2006)*.

However, the natural capacity of collaterals to remodel and enlarge to compensate for the reduced flow that occurs after occlusion of a major artery is rarely sufficient to restore maximal flow capacity to levels required under various stress-conditions. In the late stages of peripheral vascular disease, progression of tissue hypoperfusion results in ischemic ulceration and gangrene. Unfortunately, amputation is required in more than a third of these patients *(Mi Hyang et al., 2006)*.

Rapid revascularization of injured, ischemic, and regenerating organs is essential for the restoration of their physiological function *(Mi Hyang et al., 2006)*.

Although both surgical bypass and endovascular procedures remain effective in improvement of the

blood flow in the ischemic legs, not all the patients are candidates for intervention. The effort in basic science laboratories has showed us the safety of the therapeutic angiogenesis *(Reis, 2005)*.

Stem cell-based regenerative medicine therapies have been touted recently as a noveltherapeutic approach to treat and cure a wide range of diseases. Both adult and stem (ES) cells can serve important sources of precursor cells to derive more mature cell potentially utilized for clinical applications *(Peiman et al., 2005)*.

Therapeutic angiogenesis, the process of growing collateral blood vessels to better perfuse ischemic tissue, has been hailed as an up-and-coming treatment for symptomatic lower-extremity peripheral arterial occlusive disease *(Hwang et al., 2007)*.

A minimally invasive durable treatment would be welcome since current treatment options for this disease carry high risk, limited efficacy or limited durability *(Hwang et al., 2007)*.

Bone marrow is a rich reservoir of tissue-specific stem and progenitor cells. Experimental and clinical studies have shown that endothelial progenitor cells are mobilized from bone marrow, migrate to ischemic

tissue, and contribute to the neovascularization process in response to tissue ischemia.In patients suffering from peripheral arterial disease (PAD), such as arteriosclerosis obliterans (ASO) and thrombo-angitis obliterans (Buerger's disease), the implant-tation of autologous whole bone marrow mononuclear cells into the gastrocnemius muscle resulted in significant improvements of limb blood flow *(Akio Ishida, 2005)*.

AIM OF THE STUDY

The aim of this study is to outline the pathophysiology that is responsible of peripheral arterial disease, stem cell therapy as a new choice for treatment, and to point out different techniques for stem cell injection.

EMBRYOLOGY OF VASCULAR SYSTEM

Initial development of the vascular system

The primitive vascular system forms initially from a clump of mesenchymal cells that separate and form channels. These channels eventually unite to form primitive endothelium-lined vessels that become a functioning vascular network by the end of the third week. This system then connects to the developing heart that, although it consists only of two tubes, is still capable of effectively circulating blood *(Joseph Giordano; 2005)*.

At the beginning of the fourth week, the cardiovascular system consists of two heart tubes connected to a paired dorsal aorta that extends down the entire length of the embryo. The dorsal aortas each have segmental dorsal, lateral, and ventral branches. At the level of the seventh cervical vertebra, the paired dorsal aortas fuse distally to create the thoracic aorta and abdominal aorta; proximal to the seventh cervical vertebra, however, the paired dorsal aortas persist. As the aortic fusion occurs, the heart tubes fuse to form the heart. Cephalad to the developing heart, the truncus arteriosus and the aortic sac form. Six pairs of arteries, called ***aortic***

arches, develop from the aortic sac, pass laterally around the developing gut, and connect to the paired dorsal aorta *(Joseph Giordano; 2005)*.

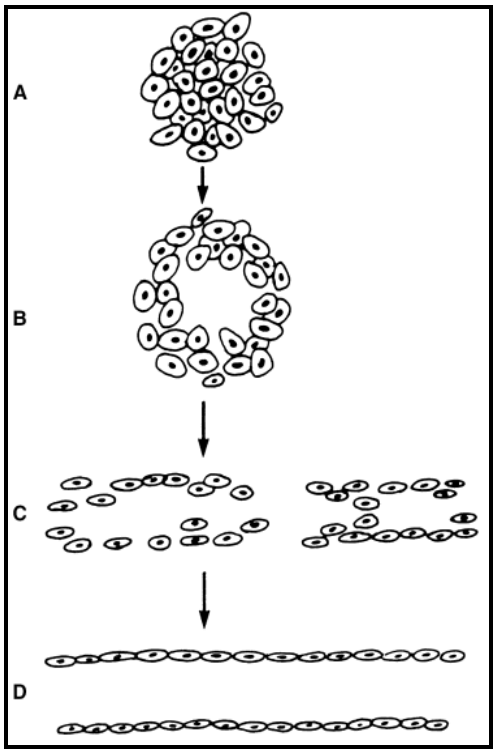

Fig. (1): Initial development of vessels. **A,** Clumps of cells forms. **B,** Cavities develop. **C,** Channels form. **D,** Channels unite to form primitive endothelium-lined vessels *(Joseph Giordano, 2005).*

The Extremities

Each upper and lower extremity begins as an outgrowth of tissue, a limb bud, off the trunk of the embryo. Initially, the limb bud is nourished by a capillary plexus that coalesces to form a single artery as the limb elongates *(Joseph Giordano, 2005)*.

The development of the arterial supply to the ***lower extremities*** is more complicated than that in the

upper extremity. Two systems develop. The *sciatic* system forms initially *(Am Anat; 1919)*.

The proximal part of the fifth lumbar dorsal segmental artery becomes the common iliac artery. The internal iliac arteries arise from the common iliac arteries *(Joseph Giordano, 2005)*.

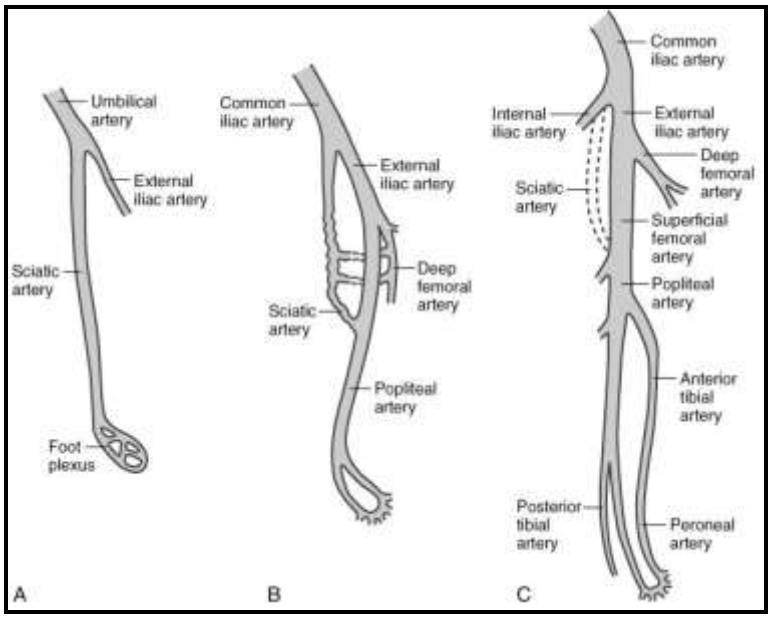

Fig. (2): Arterial supply to the left lower extremity. **A,** Sciatic artery forming as a branch of the umbilical artery initially supplies the entire leg. **B,** The sciatic artery regresses, and the external artery develops into the common femoral artery to supply the thigh. Note that the sciatic artery communicates with the popliteal artery just above the knee. **C,** The sciatic artery disappears, although small portions remain to form the popliteal and peroneal arteries *(Joseph Giordano, 2005).*

The umbilical artery joins the internal iliac artery. The sciatic arteries develop from the internal iliac arteries following the posterior course of the

sciatic nerve. In the lower thigh, the sciatic artery joins the iliofemoral system at the popliteal level. *(Joseph Giordano, 2005)*.

At the sixth week of gestation, the second system of the lower extremity, the ***external iliac artery***, develops off the umbilical artery and grows to become the iliofemoral system. The iliofemoral system replaces the sciatic system, which regresses almost completely. In the leg, segments of the sciatic artery persist, forming parts of the popliteal and peroneal arteries. In the pelvis, remnants of the sciatic system form the internal iliac artery and its branches, the inferior and superior gluteal arteries *(Joseph Giordano, 2005)*.

The popliteal artery forms from the union of two arteries, (1) the ***deep popliteal artery***, which is part of the sciatic system initially supplying blood to the lower leg, and (2) the later-developing ***superficial popliteal artery***. The distal section of the deep popliteal artery anterior to the popliteus muscle regresses. The superficial popliteal artery forms posterior to the popliteus muscle and unites with the proximal part of the deep popliteal artery to form the mature popliteal artery *(Joseph Giordano, 2005)*.

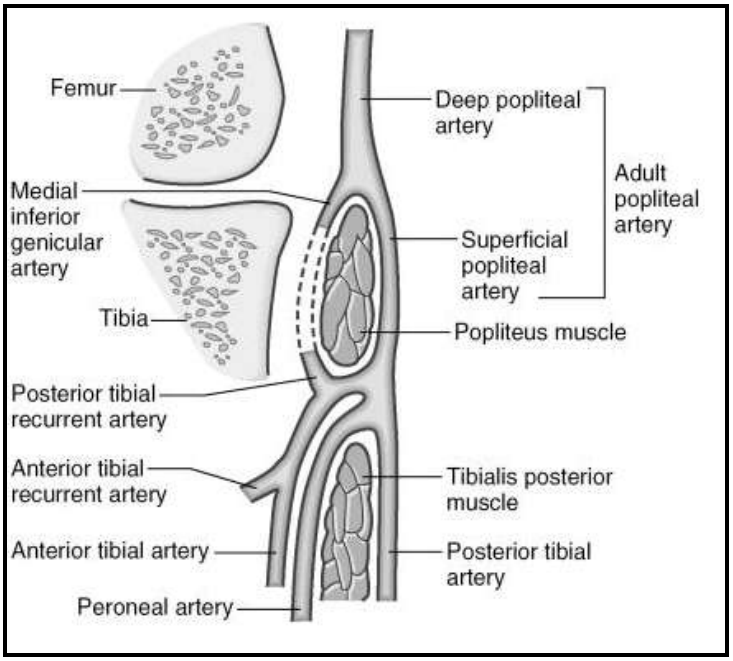

Fig. (3): Embryologic development of the popliteal artery, as modified from Senior (Am J Anat 25:55, 1919). The deep popliteal artery anterior to the popliteus muscle regresses, and the superficial popliteal artery posterior to the popliteus muscle becomes the mature popliteal artery ***(From Gibson Let al., 1977)***.

Lower Extremity Vascular Anomalies

Persistent Sciatic Artery

If the femoral system fails to develop, the sciatic artery may persist instead of regressing, supplying blood to the thigh. The incidence of this rare anomaly is 0.05% ***(Mayschak et al., 1984)***.

The sciatic artery may be complete from its origin off the internal iliac artery to its union with the popliteal artery. It may also be incomplete, so that it connects

with the internal iliac or popliteal artery through small collaterals. The anomalous persistent sciatic artery is anatomically next to the sciatic nerve, entering the thigh through the sciatic notch and remaining posterior to the adductor magnus until the insertion of that muscle, where it enters the popliteal fossa to join the popliteal artery *(Joseph Giordano, 2005)*.

If the artery is complete, the patient with a persistent sciatic artery may present with a palpable popliteal artery but absence of a femoral pulse. A persistent sciatic artery in the buttocks is superficial and can be traumatized by normal activity, such as sitting *(McLellan et al., 1982)*.

Popliteal Entrapment Syndrome

The popliteal entrapment syndrome is an anomaly that results from the delayed attachment of the medial head of the gastrocnemius muscle *(Gibson et al., 1977)*.

The lateral head attaches first to the lateral epicondyle of the femur, and the medial head attaches later to the medial epicondyle. At the time of the attachment of the medial head, the popliteal artery has already formed and is in its normal anatomic location *(Joseph Giordano, 2005)*.

If the popliteal artery develops late or if the medial head migrates early, the artery is not in its normal location; instead, it is swept medially and impinged against the femur as the medial head attaches to the epicondyle. Actually, no case of compression of the popliteal artery on the lateral epicondyle has been observed, probably because the lateral head attaches early, well before the popliteal artery forms. Clinically, patients present at an early age compression of the artery against the femur by the medial head of the gastrocnemius muscle, causes claudication and popliteal artery aneurysm formation *(Joseph Giordano, 2005)*.

Structure of the Artery

Composition of Arteries

The principal organized constituents of the arterial wall are the smooth muscle cells and the extracellular matrix, composed of elastin, collagen, and ground substance. These components are present in various quantities, orientations, and interconnect-tions along the vascular tree. Because the mechanical properties of a material depend on its composition, structure, and microstructure, the arterial wall exhibits a wide range of behaviors depending on the location in the body *(Michel Labrosse, 2007)*.

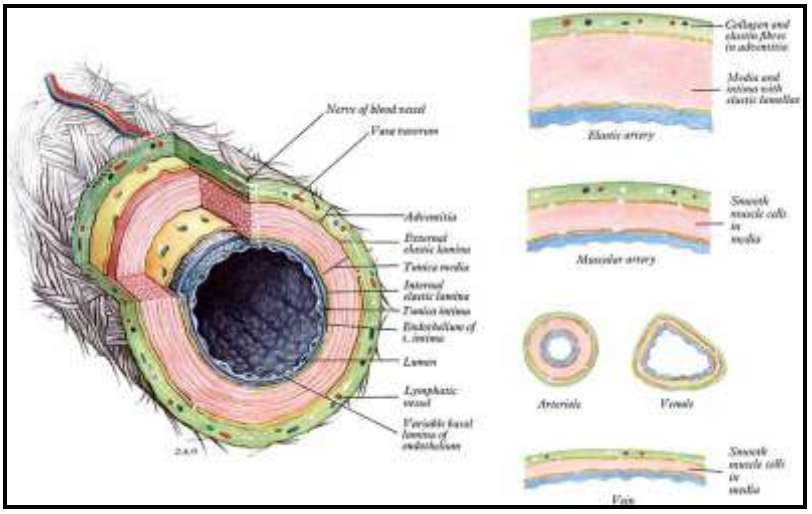

Fig. (4): Schematic drawing showing the principal structural features of the larger blood vessels. On the left the major layers and associated features of a muscular artery are depicted. On the right the particular features of an elastic artery, a muscular artery, an arteriole, a venule and a vein are shown, as they appear in transverse sections of these vessels *(Gray's anatomy, 2005).*

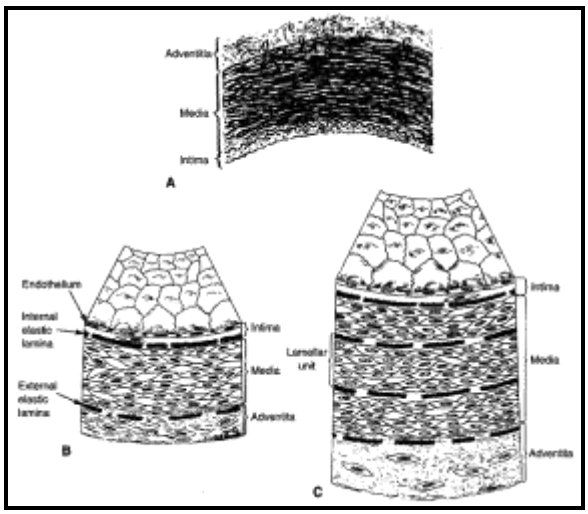

Fig. (5): (A) Cross-section of an arterial wall. (B) Normal muscular artery. (C) Normal elastic artery *(Gray's anatomy, 2005)*.

Structure of Arteries

All arteries are made of three concentric layers, or tunics: the innermost tunica intima, the middle

tunica media, and the outermost tunica adventitia *(Michel Labrosse, 2007)*.

The intima (strictly speaking the tunica intima), or innermost layer: whose main component, the endothelium, lines the entire vascular tree *(Gray's anatomy, 2005)*.

The media (tunica media), made of muscle tissue, elastic fibres and collagen; while it is by far the thickest layer in arteries, the media is absent in capillaries and is comparatively thin in veins *(Gray's anatomy, 2005)*.

The adventitia (tunica adventitia), the outer wrapping of the vessel, made of connective tissue nerves and capillaries. The adventitia links the vessels to the surrounding tissues *(Gray's anatomy, 2005)*.

The main histological components of the vessel wall are therefore an endothelium, elastic tissue, muscle tissue, collagen and connective tissue *(Gray's anatomy, 2005)*.

Endothelium

The lumen of all blood vessels is lined by endothelial cells which maintain the fluidity of the

blood, regulate the interactions of circulating cells and platelets with the vessel walls and form the interface between the bloodstream and extravascular tissues *(Gray's anatomy, 2005)*.

The endothelium is a monolayer of flattened polygonal cells which extend continuously over the luminal surface of the entire vascular tree. The endothelium is a key component of the vessel wall because it serves several major physiological roles, as listed below *(Gray's anatomy, 2005)*.

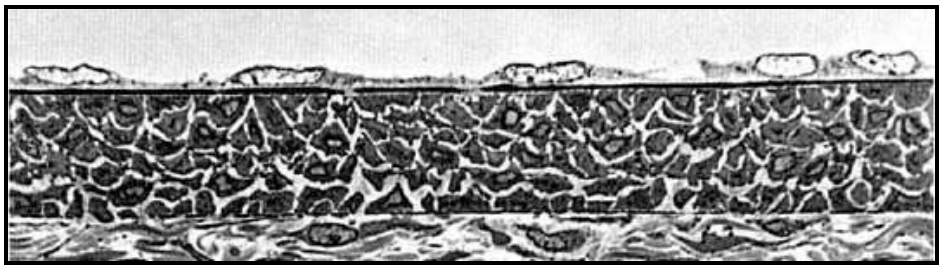

Fig. (6): Histological sections of a muscular artery, fixed in situ in a condition of physiological distension. The endothelial cells can be seen, somewhat elongated in the direction of the blood flow; Magnification x 510 *(Gray's anatomy, 2005)*.

Endothelial cells are wide and thin, tile-like and slightly curved to fit the curvature of the vessel. They are somewhat elongated in the direction of blood flow, especially in arteries *(Gray's anatomy, 2005)*.

The thickness of endothelial cells is maximal at the level of their nucleus, where it can reach 2-3μm, this part of the cell often bulging slightly into the

lumen. Elsewhere, the endothelial cell is thinner and laminar *(Gray's anatomy, 2005)*.

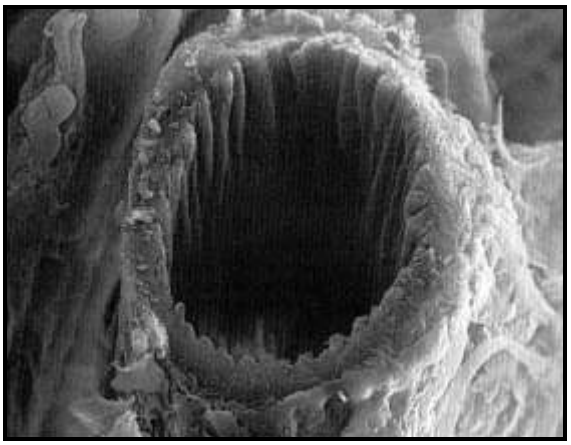

Fig. (7): A small vessel approaching the surface of the brain, examined by scanning electron microscopy. The free surface of the endothelium is corrugated by the relief of the endothelial cells. Magnification x 750 *(Gray's anatomy, 2005)*.

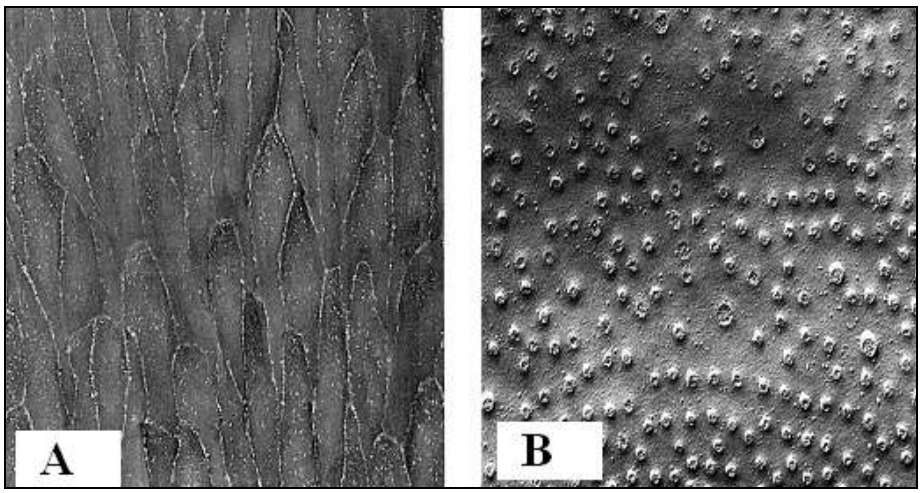

Fig. (8): **(A)** Inner surface of the endothelium of a basilar artery, examined by scanning electron microscopy. The lumenal surface is tessellated by endothelial cells which are tightly packed and elongated in the direction of the blood flow. Magnification x 1250 (Supplied by Masoud Alian of University College London.) **(B)** Freeze-fracture preparation of the plasma membrane of an endothelial cell. The E-face of the membrane shows innumerable caveolae fractured at the level of their neck. Magnification x 40000. *(Gray's anatomy, 2005)*.